UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/716,531	09/19/1996	YANN MAHE	016800-111	5887

21839 7590 12/16/2003

BURNS DOANE SWECKER & MATHIS L L P
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

EXAMINER	
HUFF, SHEELA JITENDRA	

ART UNIT	PAPER NUMBER
1642	43

DATE MAILED: 12/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/716,531	MAHE ET AL.	
	Examiner	Art Unit	
	Sheela J Huff	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-11 and 16-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2 4-11 16-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☒ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The amendment filed 9/25/03 has been considered.

The objection to claim 3 is withdrawn in view of the cancellation of the claim.

All art rejections are withdrawn in view of applicant's amendment.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2 and 4 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ferreira et al US 5389615 in view of applicant's admission on page 1 of the specification, Stedman's Medical Dictionary, 24th edition (1989) p. 707-708 and 1218 and Oxford Medical Companion, ed. J. Walton, J. Barondess and S. Lock (1994) p. 969, Oluyomi et al. European Journal of Pharmacology vol. 258 p. 131 (1991) and Hiltz et al Peptides vol. 12 p. 767 (1991).

This rejection is similar to those in the previous office action, but is re-written in view of applicant's amendment to have 2 out of 3 amino acids in their D form.

The claims are directed to a method of treating inflammation by administering a therapeutically effective amount of lysine-D-proline-D-valine or D-lysine-D-proline-valine or D-lysine-D-proline-D-valine. **On page 1 of the specification, applicant defines inflammation in terms of swelling, pain, redness and warmth (Applicant's admission).** Stedman's corroborates this admission by defining inflammation in the same terms (i.e. swelling, pain, redness and warmth) (see page 707-708 of Stedman's). The state of the art defines "treatment" as "the application of remedies to disease; the general management of illness" and "to cure sometimes, to relieve often, to comfort always" (see Oxford p. 969) and the state of the art defines "relieve" as "to free wholly or partly from pain or discomfort" (Stedman's p. 1218). Taken together, treatment is defined as the general management of illness by providing relief using remedies. The relief can be either whole or **partial**. Since there are four characteristic symptoms (swelling, pain, redness and warmth) of inflammation, treatment of inflammation reads on the partial relief of inflammation and this reads on treating at least one symptom.

Ferreira et al disclose the use of tripeptides as medicaments to treat or prevent pain wherein said tripeptides are of the formula X-Pro-Y (formula I) where X can be lys or arg and Y can be any amino acid (col. 1, lines 30-50) where the preferred compounds are X=lys or D-lys (col. 2, line 22) and Y=valine (col. 2, line 31) and each of these amino acids can be in its D-form (col. 2, lines 13-17). The preferred form of pro is also D (col. 2, lines 15-17). Thus this reference suggests making tripeptides D-lys-D-pro-val and lys-D-pro-D-val. These compounds read on the tripeptides of claims 1-2, 4 and 20. In view of the state of the art definitions and applicant's admission (see above), the reference is dealing with the treatment of inflammation.

The only difference between the prior art and the reference is that the reference deals with the treatment of one facet of inflammation (ie pain) and not all four facets of

inflammation (ie swelling, pain, redness and warmth). The only other difference between that and the instant invention is the specific use of D-lys-Dpro-Dval and the combination of another known anti-inflammatory agent with the tripeptides.

Hiltz et al disclose the tripeptide lysine-proline-valine, where the lysine and/or valine are in their D form (see Table 1). This peptide was tested for anti-inflammatory activity by administering 10ug (2.6 $x10^{-8}$ M), 20ug (5.2 $x10^{-8}$ M), 40ug (1.04 $x10^{-7}$ M) and 80ug (2.08 $x10^{-7}$ M) in 0.2 ml of sterile saline (p. 768-769). These amounts read on "anti-inflammatory effective amount" as recited in claim 1 and reads on the concentration ranging from 10^{-21} M to 10^{-3} M (see specification page 6, lines 14-21). As disclosed in Table 1, Hiltz et al show, in numerical terms, the anti-inflammatory activity of the tripeptide.

Oluyomi et al disclose the use of the K(D)PV and biological equivalents thereof in pharmaceutically acceptable formulations to treat inflammatory pain (abstract, p. 134-135 and Tables 2-3). The reference further states that the peptide analogs containing the dipeptide lys-pro "constitute a novel approach to the control of pain, particularly **inflammatory** pain "(emphasis added, p. 131 second column, first full paragraph). The reference states that the peptide inhibits the release of prostaglandin and other inflammatory agents (p. 136, first column, lines 5-9 from the bottom) and additionally on page 137, first column, lines 8-11 that "this confirms the peripheral anti-inflammatory activity of this peptide' (this peptide refers to lys-D-pro-val). In view of the state of the art definitions, the reference is dealing with the treatment of inflammation.

As discussed above, the primary reference clearly suggests the making and the use of Dlys-Dpro-Dval (preferred embodiment) and D-lys-D-pro-val and lys-D-pro-D-val. Therefore, in view of this suggestion, it would have been obvious to one of ordinary skill

in the art at the time of the invention to make and use either of the three peptides to treat pain. The combination of two or more known agents to treat a disease is within the purview of one skilled in the art. Dosages are within the purview of one skilled in the art. Furthermore, on page 1 of the specification, applicant admits that inflammation includes the facets of swelling, pain, redness and warmth. Stedman's corroborates this by defining inflammation in the same terms(see page 707-708 of Stedman's). The state of the art defines "treatment" as "the application of remedies to disease; the general management of illness" and "to cure sometimes, to relieve often, to comfort always" (see Oxford p. 969) and the state of the art defines "relieve" as "to free wholly or partly from pain or discomfort" (Stedman's p. 1218). Taken together, treatment is defined as the general management of illness by providing relief using remedies. The relief can be either whole or **partial**. Since there are four characteristic symptoms (swelling, pain, redness and warmth) of inflammation, treatment of inflammation reads on the partial relief of inflammation and this reads on treating at least one symptom. Therefore, in view of the state of the art definition of "treatment", it would have been obvious to one of ordinary skill in the art at the time of applicant's invention that the Ferreira et al peptide be used to treat inflammation.

Furthermore, Hiltz et al further supports the examiner's position. As shown in Hiltz et al peptides made with D-lys11 or D-val13 or D-lys11 and D-val13 (pages 769-770) show that the changes of the Lys and/or val to its D-form does not abolish anti-inflammatory activity. This further supports the Ferreira et al reference in that either val or lys can be in its D form and activity is retained. Oluyomi et al also provides further

support in that it discusses the Hiltz et al reference on page 137 and discusses the different stages of inflammation and that the tripeptide with the D-pro was significantly active in the late phase but not in the early phase. Thus, the primary reference, taken together with what is known in the state of the art makes applicant's invention obvious.

Claims 1-2, 4-6 and 19-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ferreira et al US 5389615, applicant's admission on page 1 of the specification, Stedman's Medical Dictionary, 24th edition (1989) p. 707-708 and 1218 and Oxford Medical Companion, ed. J. Walton, J. Barondess and S. Lock (1994) p. 969 in view of Lipton US 5157023, Hiltz et al Peptides vol. 12 p. 767 (1991) and Oluyomi et al. European Journal of Pharmacology vol. 258 p. 131 (1991).

The primary references and the combination of the primary references and Oluyomi et al and Hiltz et al have been discussed above.

The only difference between that and the instant invention is the use of protecting groups.

Lipton disclose the use of protected peptides (specifically acetyl-KPV) and that the use of protected peptides is preferred because the protection group can confer stability to the peptide by decreasing the problems of enzymatic attack and degradation and also discloses that the protected tripeptide is more active than the unprotected form (col. 4, lines 58-68).

Therefore, in view of the enhanced activity of the protected peptide over the unprotected peptide, it would have been obvious to one of ordinary skill in the art at the

time of the invention to use a protecting groups, such as acetyl, to protect the tripeptides of the primary reference to confer stability to the tripeptides. It is noted that the tripeptides of the primary and secondary references are related (see Oluyomi et al p. 131 which discloses that amino acids 193-195 of IL-1beta are KPV and that amino acids 11-13 of alpha MSH are KPV and that these peptides are related).

Claims 1-2, 4-11 and 16-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ferreira et al US 5389615, applicant's admission on page 1 of the specification, Stedman's Medical Dictionary, 24th edition (1989) p. 707-708 and 1218 and Oxford Medical Companion, ed. J. Walton, J. Barondess and S. Lock (1994) p. 969 in view of Nordlund et al US 4874744, Lipton US 5157023 and Remington's Pharmaceutical Science Ch 87 and 92, Hiltz et al Peptides vol. 12 p. 767 (1991) and Oluyomi et al. European Journal of Pharmacology vol. 258 p. 131 (1991).

The primary references and the combination thereof have been discussed above.

The only difference between the instant invention and the reference is (1) the use of the tripeptide in a topical formulation, (2) the use of a protecting group, (3) the specific mention of Dlys-Dpro-Dval and (4) the combination of another known anti-inflammatory agent with the tripeptides.

As discussed above, the primary reference clearly suggests the making and use of D-lys-Dpro-Dval (preferred embodiment).

Lipton disclose the use of protected peptides (specifically acetyl-KPV) and that the use of protected peptides is preferred because the protection group can confer stability to the peptide by decreasing the problems of enzymatic attack and degradation and also discloses that the protected tripeptide is more active than the unprotected form (col.. 4, lines 58-68).

Nordlund discloses that alpha MSH can be applied topically to treat inflammatory skin diseases such as dermatitis in a concentration of 10-2M/cm2 to 10-10M.cms (abstract, col. 1, lines 5-41, summary of the invention, col. 2, lines 33-65). The pharmaceutical formulation includes ointments and creams (col.. 2, lines 50-55). Remington's is cited to show that formulation of topical treatments and aerosols is well known in the art.

Therefore, in view of the suggestion of the primary reference to make and use D-lys-D-pro-D-val, it would have been obvious to one of ordinary skill in the art at the time of the invention to make and use D-lys-D-pro-Dval to treat pain. It also would have been obvious to one of ordinary skill in the art to use a protecting groups, such as acetyl, to protect the tripeptides of the primary reference to confer stability to the tripeptides. It is noted that the tripeptides of the primary reference and secondary references are both derived from amino acids 11-13 of alpha MSH. It also would have been obvious to use the tripeptides of the primary reference to treat inflammatory disorders of the skin and to make formulations suitable for topical administration because according to Nordlund et al MSH is used to treat such disorders and the tripeptides of the primary reference are amino acids 11-13 of MSH (see Oluyomi et al p. 131 which discloses that amino acids 193-195 of Il-1beta and that amino acids 11-13 of alpha MSH are KPV and that these peptides are related). The combination of two or more known agents to treat a disease is within the purview of one skilled in the art. Dosages are within the purview of one skilled in the art.

Conclusion

Applicant's amendment to require 2 out of 3 amino acids be in their D form necessitated the new ground(s) of rejection presented in this Office action. Accordingly,

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheela J Huff whose telephone number is 703-305-7866. The examiner can normally be reached on Tuesday 5:30am-11:30am and Fridays 6:00am-4:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone number for the organization where this application or proceeding is assigned is 703-308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Sheela J Huff
Primary Examiner
Art Unit 1642